PREDNISOLONE ACETATE-ELUTING NOVEL BIODEGRADABLE VASCULAR STENTS FOR IMPLANTATION

Pharm. (M.Sc.) Can Sarisozen

Assist. Prof. Dr. Betul Arica, Prof.Dr. Sema Calis, Prof.Dr. A.Atilla Hincal

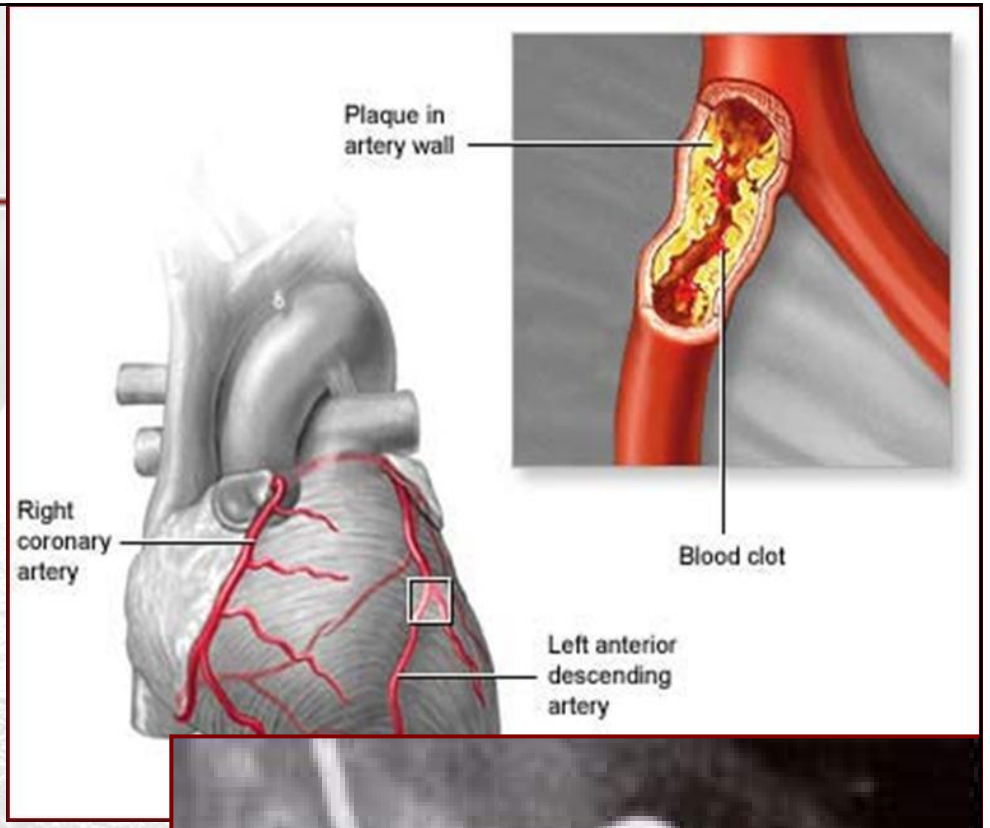
Hacettepe University, Faculty of Pharmacy,
Department of Pharmaceutical Technology, 06100 Sıhhiye, Ankara TURKEY

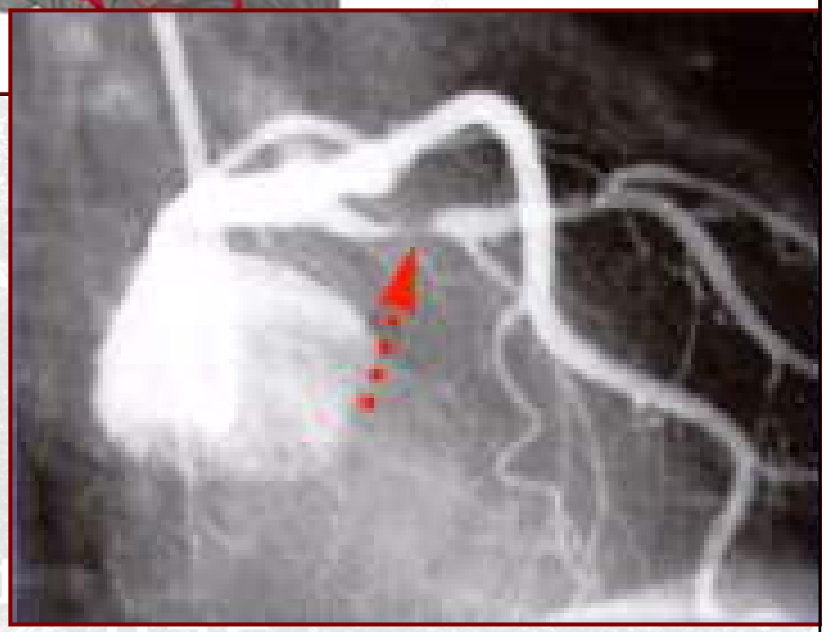
Coronary Artery Disease (CAD)

- CAD is the leading cause of death in the Western World for men and women
- CAD is narrowing of the small blood vessels that supply blood and oxygen to the heart (coronary arteries).
- Coronary disease usually results from the build-up of fatty material and lessions called plaque.

Atherosclerosis

- Atherosclerosis is an intimal disease which fatty material collects along the walls of arteries.
- *stenosis*
- As the coronary arteries narrow, the flow of blood to the heart can slow or stop.

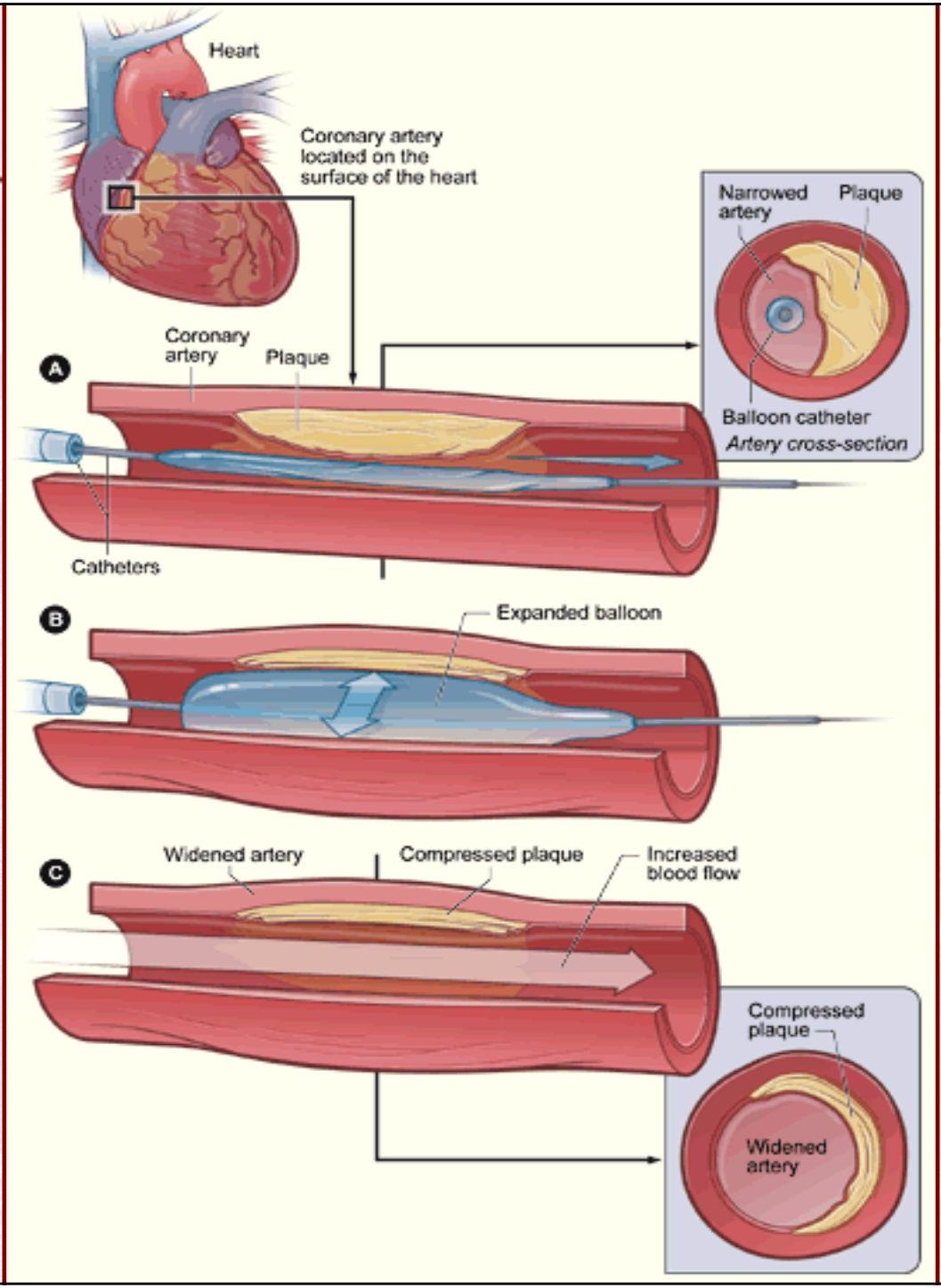




Treatment

- For overcome this problem Percutaneous Transluminal Coronary Angioplasty *(PTCA)* was introduced in the last period of 70's and has become a common method for treating coronary arterial stenosis.

- A balloon is used to open narrowed or blocked blood vessels of the heart coronary arteries


Heart
Coronary artery located on the surface of the heart
Narrowed artery
Plaque
Balloon catheter
Artery cross-section
Coronary artery
Plaque
A
Catheters
B
Expanded balloon
C
Widened artery
Compressed plaque
Increased blood flow
Compressed plaque
Widened artery

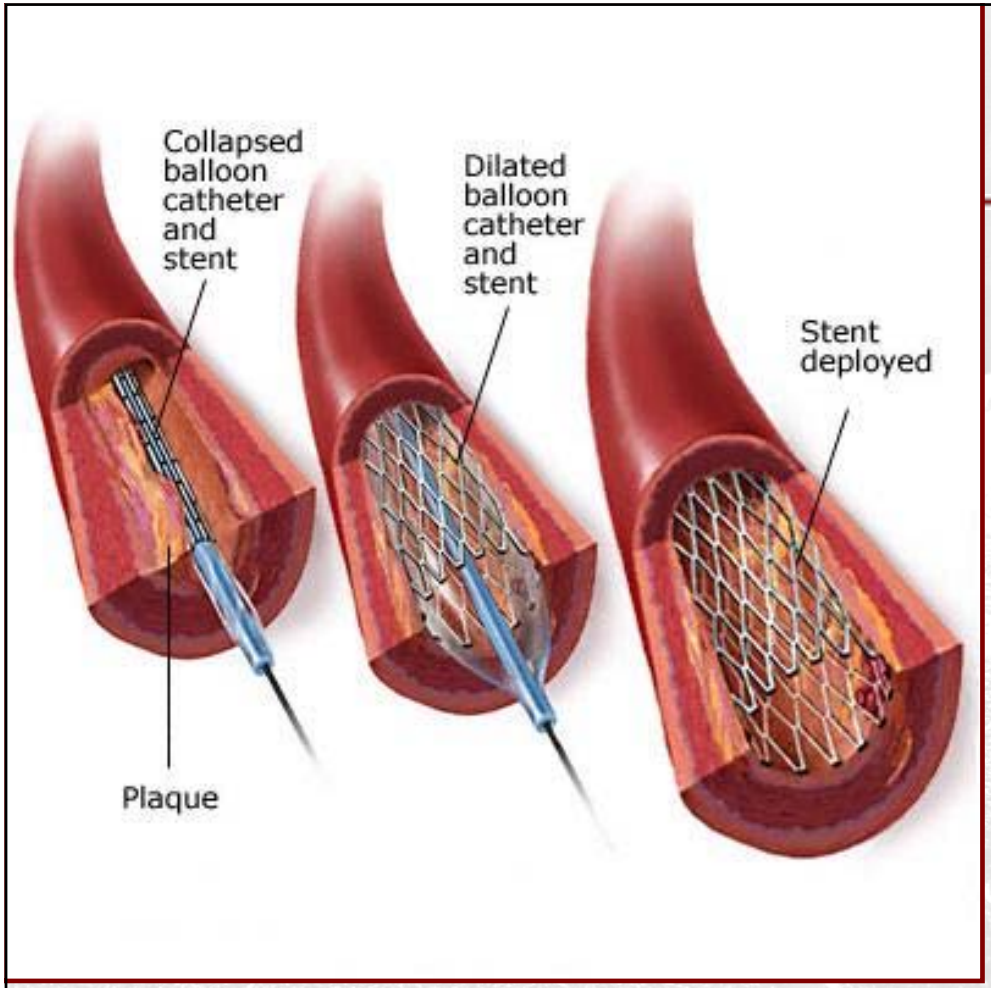
- PTCA with a balloon has a major limitation called ***restenosis*** which is the maladaptive response of the coronary artery to injury and characterized by re-narrowing of the artery after the angioplasty.

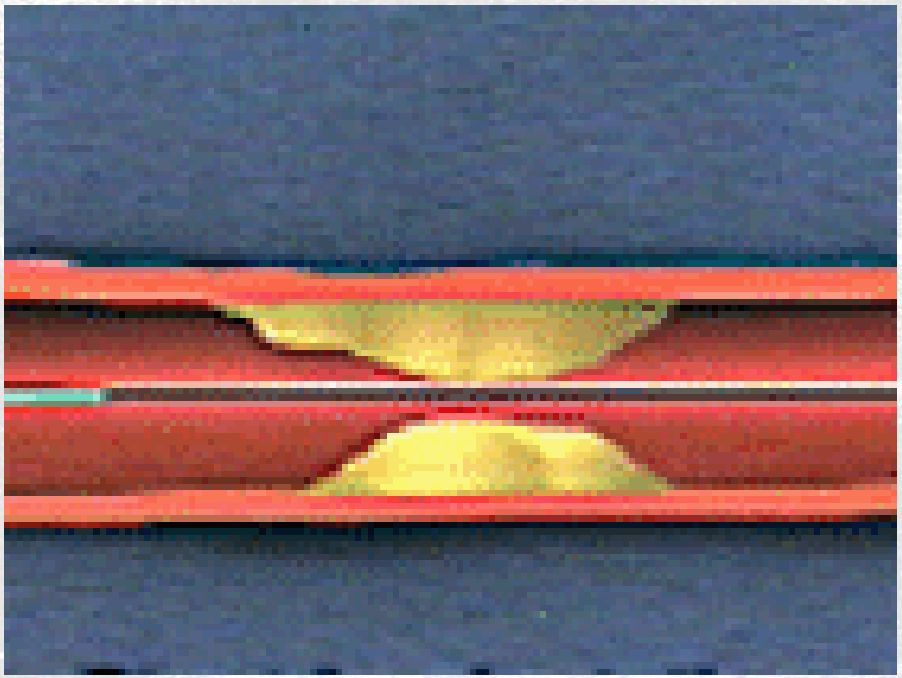
- Restenosis can be described currently as consisting of two components: first called “elastic recoil” and the second component called “neointimal hyperplasia”

Stents

- Stent is a small, metal tube that is inserted permanently into an artery.

- Acts as a scaffold, remaining in place permanently to help ***keep the artery open***.


Collapsed balloon catheter and stent
Dilated balloon catheter and stent
Stent deployed
Plaque



- Restenosis rates in patients who have stents implanted are 20–40%.

In-Stent restenosis

Metallic bare stents - Not Enough

Drug Eluting Stents (DES)

- DES provide both mechanical scaffolding and local delivery of a pharmacological agent.
- DES reduced the in-stent restenosis rates
- The need of a stent? Safety?
- **Biodegradable Polymeric Stents**

Aim

- Prednisolone Acetate (PA) – model drug

- Biodegradable Stent Formulations;
  - PA was incorporated into the film based polymeric biodegradable stents to provide controlled local release of the drug during the mechanical support phase
  - Also PA containing spray-dried chitosan microspheres were incorporated into the stents

Chitosan Microspheres

- 2^2 Factorial design was used and 8 microsphere formulations were developed and characterized.

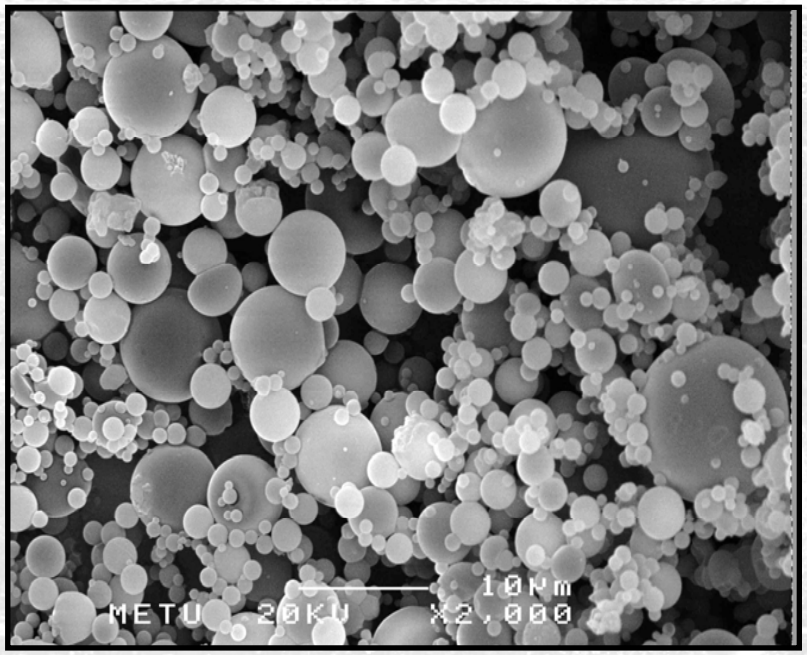
Formulation Code	Polymer Type	Polymer Concentration (%)	Targeted Encapsulation Amount (%)
CL0,5PA10	Low M_w	0,5	10
C			
C			
C			
C			
CM0,5PA20	Medium M_w	0,5	20
CM1PA10	Medium M_w	1	10
CM1PA20	Medium M_w	1	20

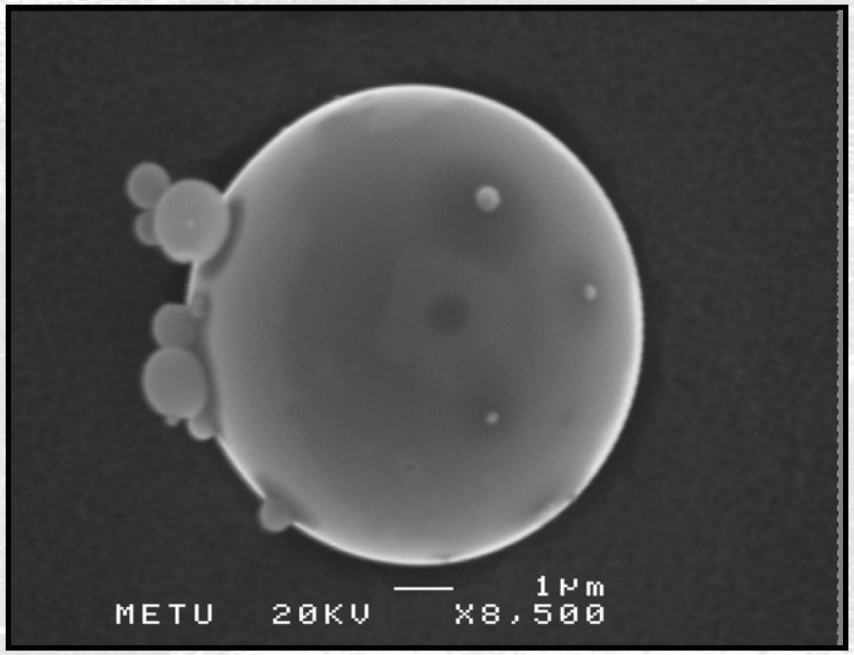
Formulation Code	Polymer Type	Polymer Concentration (%)	Targeted Encapsulation Amount (%)
CM1PA20	**Medium M_w Chitosan**	**1**	**20**

Mean Particle Size: **10.41 ± 0.03 µm**

In vitro release time: **11 Days**

(100% Cumulative PA Release)

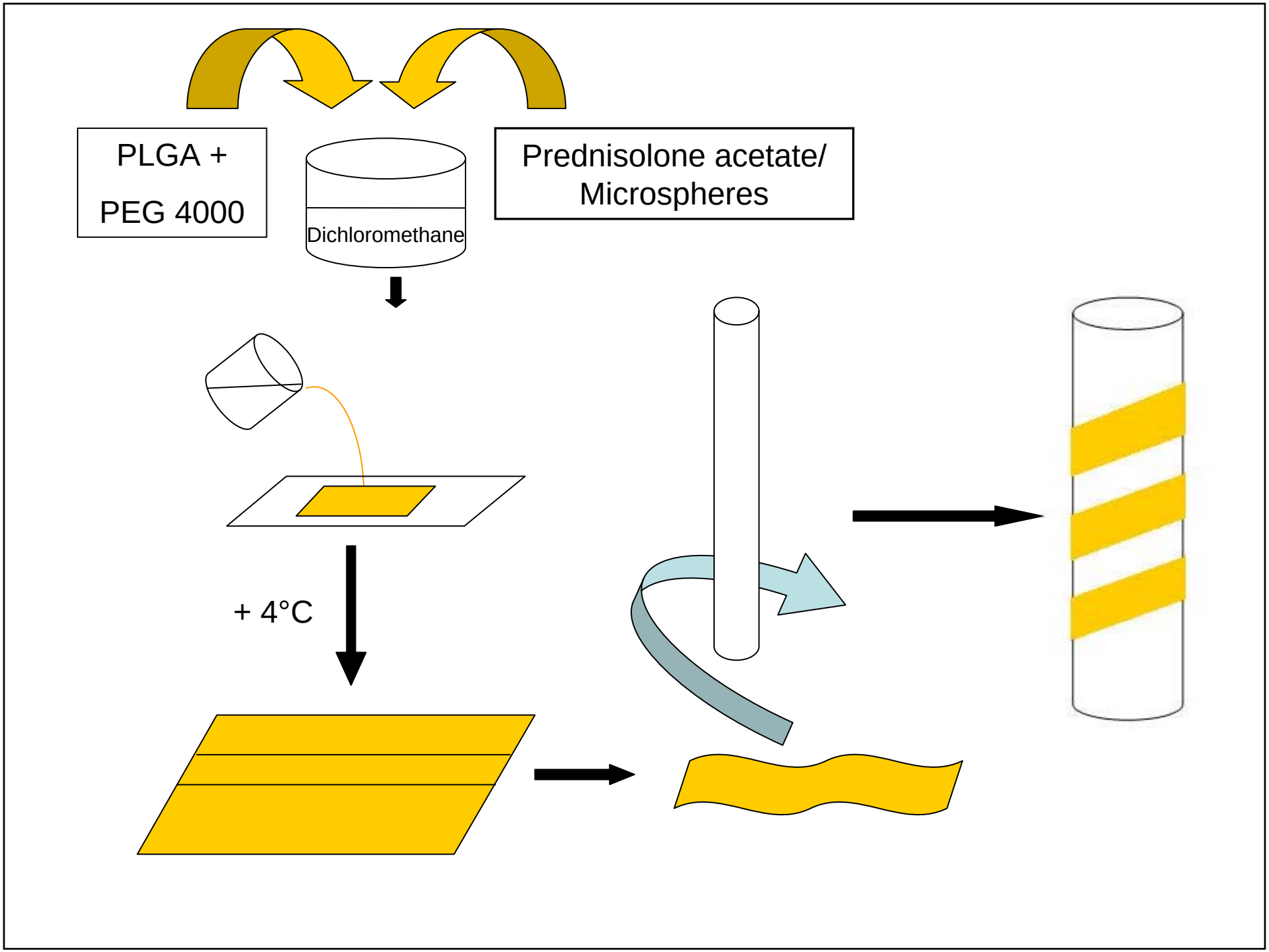




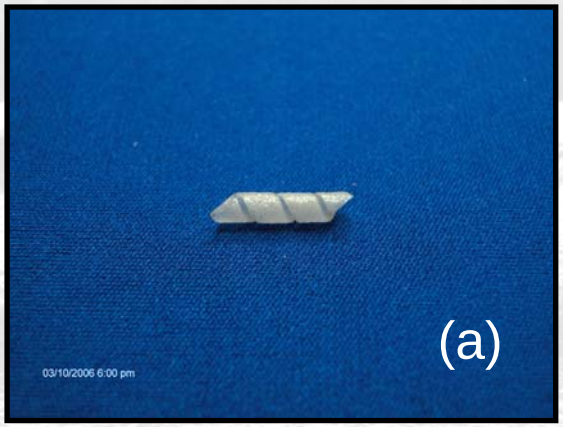
Preparation of Biodegradable Polymeric Stents

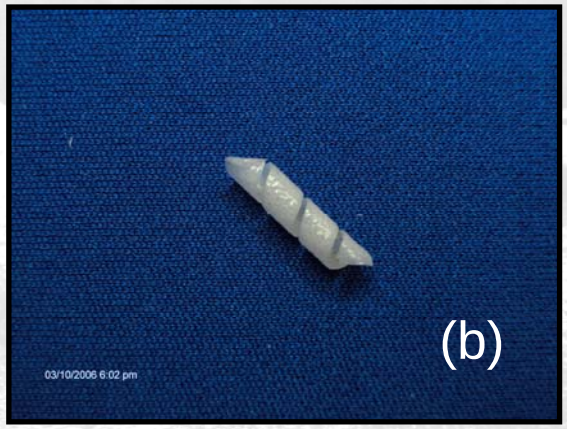
- PLGA (75:25)
- PLGA (50:50)
- Solution-Casting Method

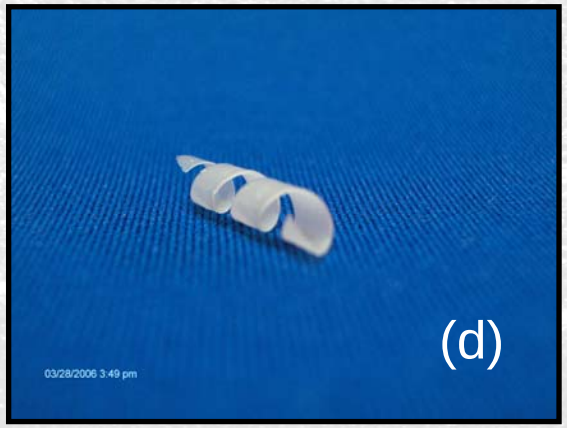
Formulation Code	Polymer	PA or Microspheres
S1	PLGA (75:25)	PA Incorporated
S2	PLGA (75:25)	Microsphere Incorporated
S3	PLGA (50:50)	PA Incorporated
S4	PLGA (50:50)	Microsphere Incorporated


PLGA +
PEG 4000
Dichloromethane
Prednisolone acetate/
Microspheres
+ 4°C

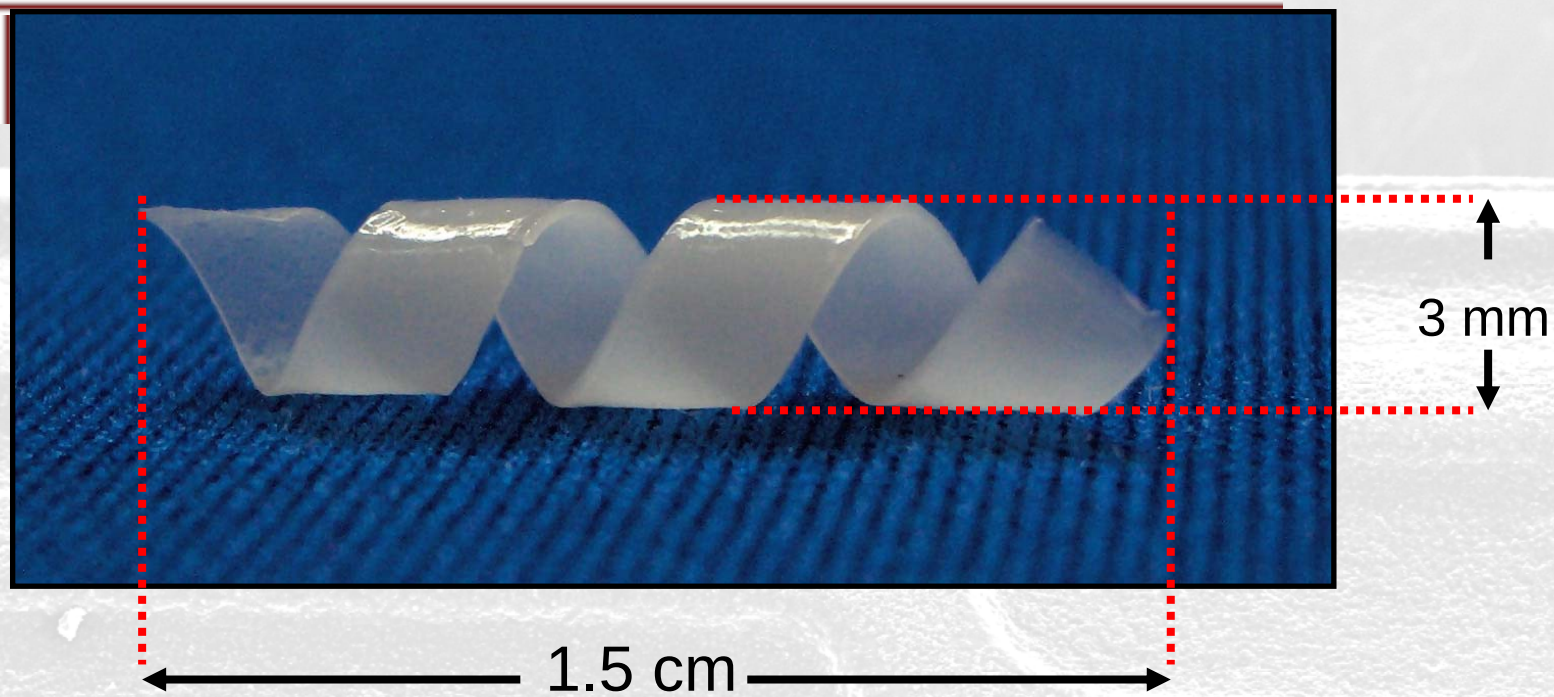
Surface and Morphology of the Stents







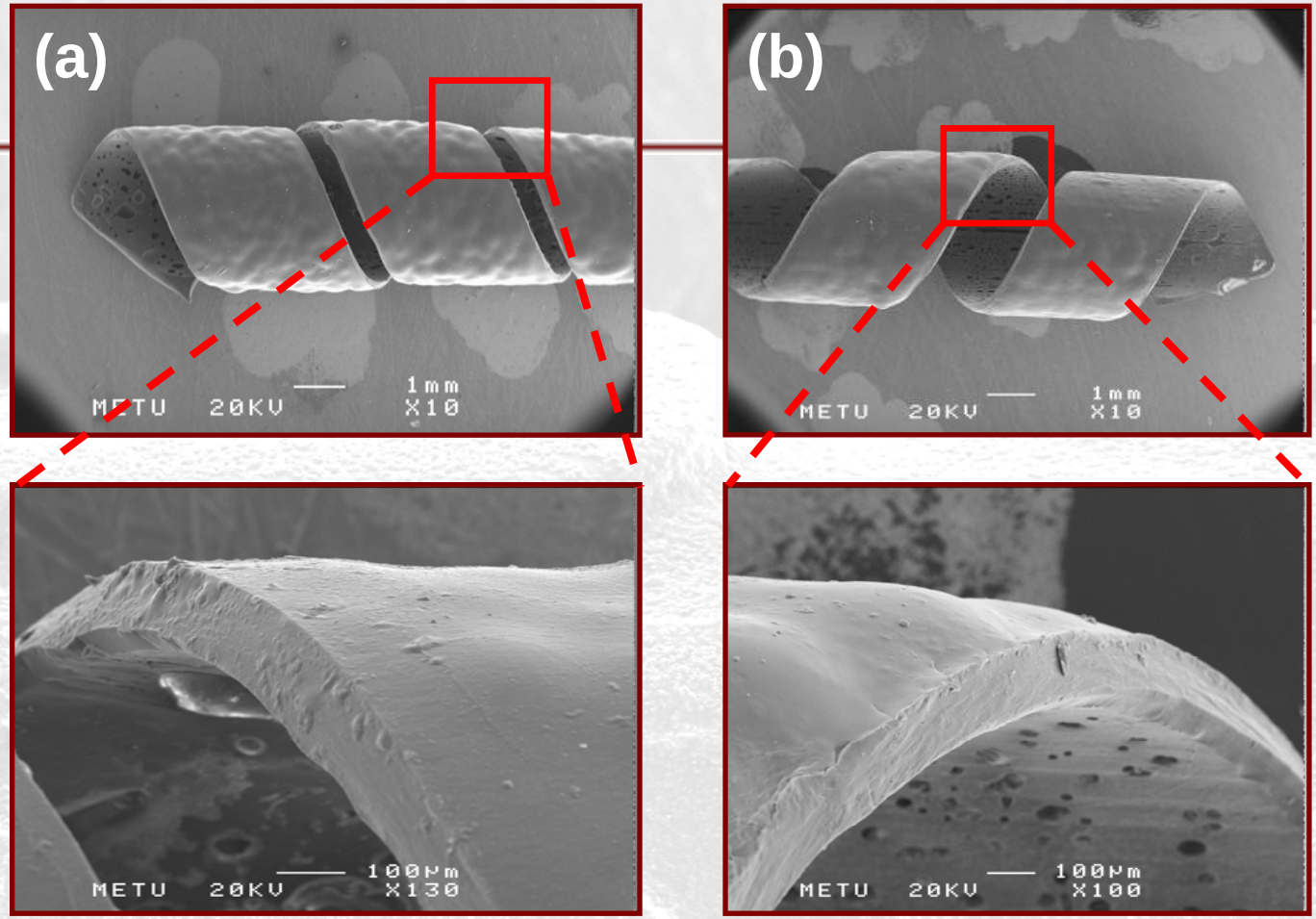
PA incorporated (a) and PA containing chitosan microspheres incorporated (b) PLGA (75:25) stents, PA incorporated (c) and PA containing chitosan microspheres incorporated (d) PLGA (50:50) stents



The polymer wall thickness was

136.5 ± 5 µm - PLGA (75:25) stents

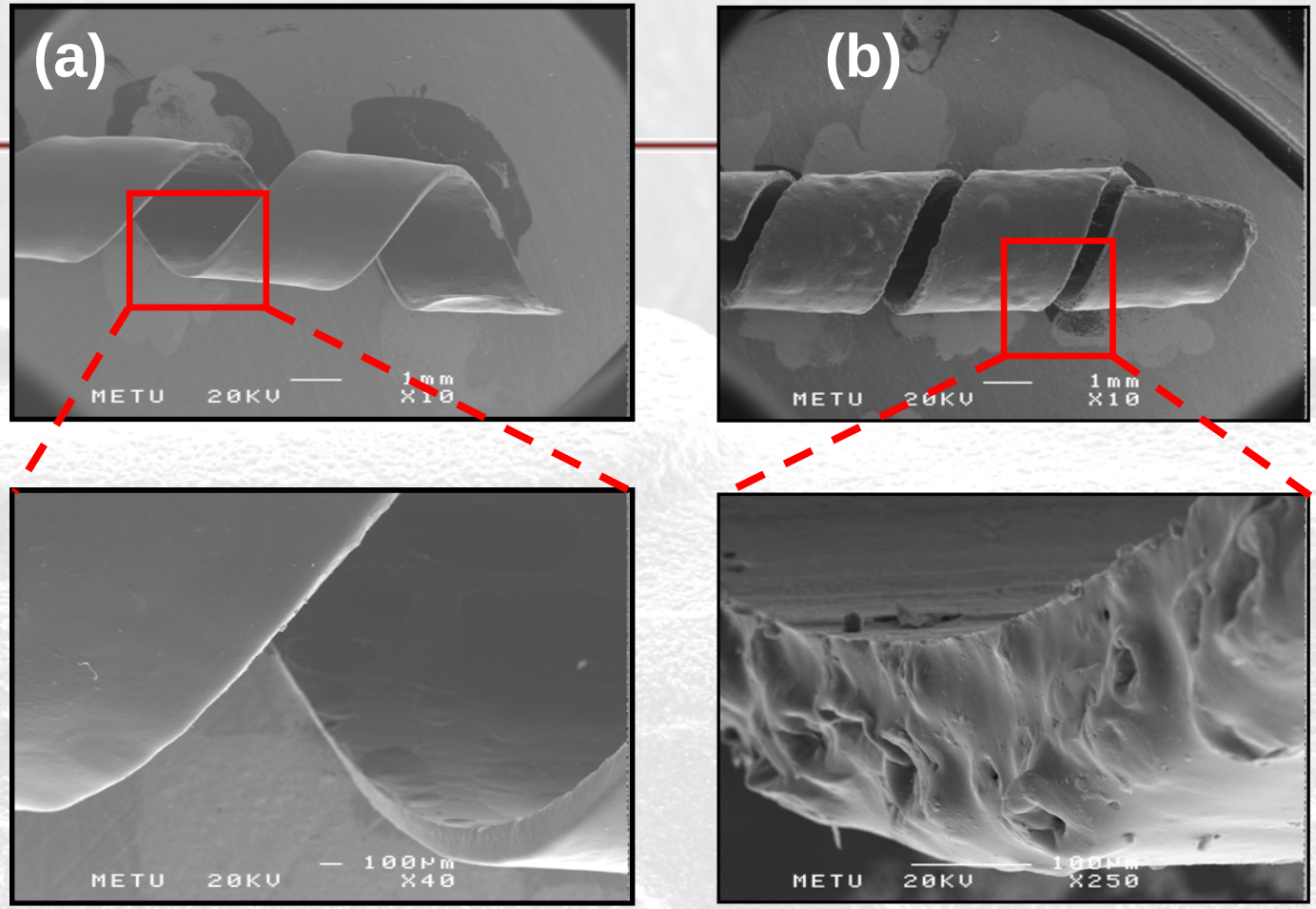
109 ± 8 µm - PLGA (50:50) stents



PA incorporated (a)

PA containing chitosan microspheres incorporated (b)

PLGA (75:25) stents



PA incorporated (a)

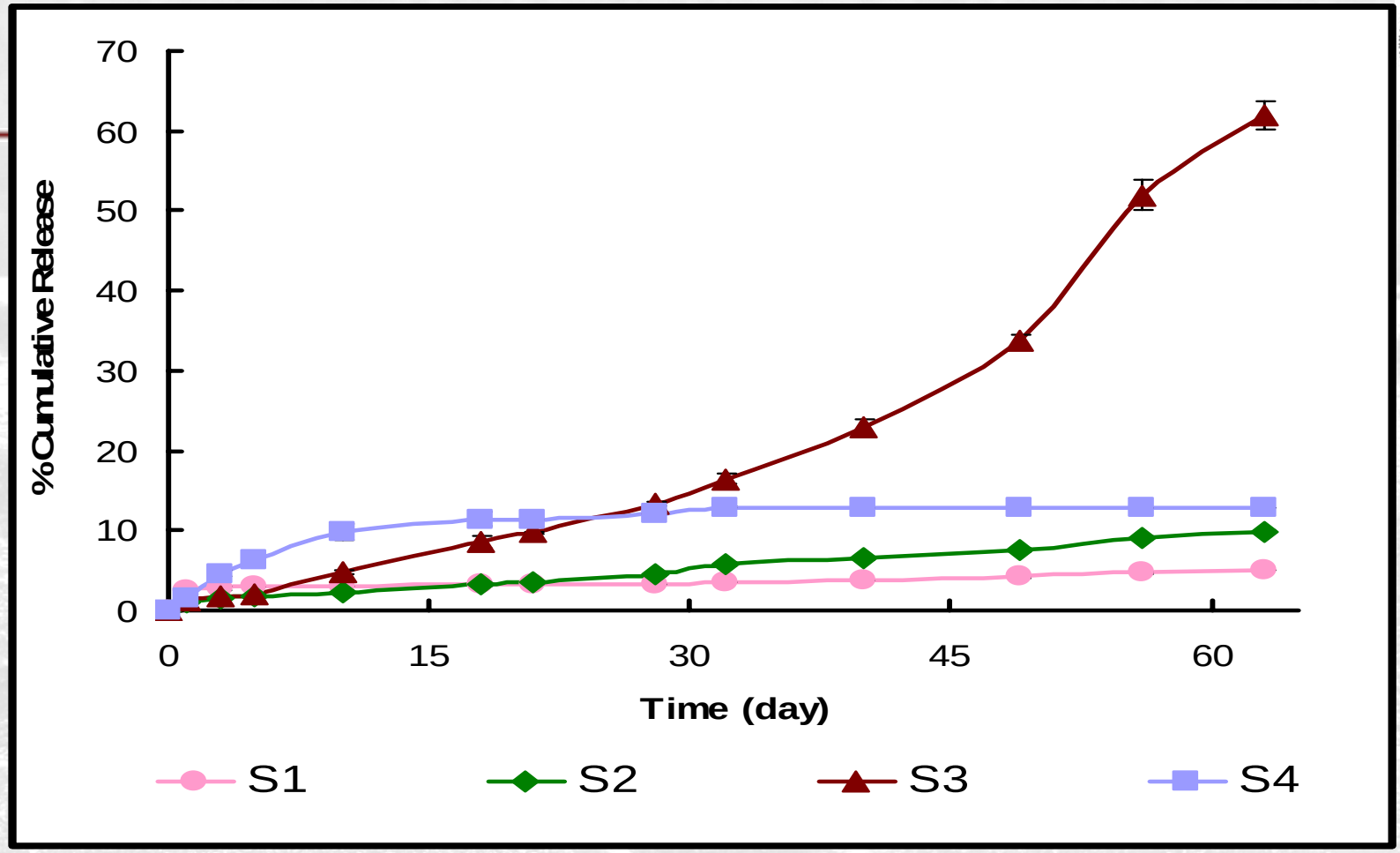
PA containing chitosan microspheres incorporated (b)

PLGA (50:50) stents

In Vitro Release

- 2 mL of 0.5% (w/v) sodium lauryl sulfate and 0.05% (w/v) sodium azide containing Phosphate Buffered Saline (PBS) pH 7.4

- The stents were shaken in Eppendorf tubes in a horizontal shaker at 50 rpm, at 37°C



Formulation Code	Polymer	PA or Microspheres
S1	PLGA (75:25)	PA Incorporated
S2	PLGA (75:25)	Microsphere Incorporated
S3	PLGA (50:50)	PA Incorporated
S4	PLGA (50:50)	Microsphere Incorporated

Conclusion

- By using biodegradable PLGA (75:25) and PLGA (50:50) polymers, cardiovascular stents were manufactured and characterized.

- Different release profiles were obtained with using different polymers.

- The released amount of PA from the PLGA (50:50) stents (with PA only or PA containing microspheres) was always higher

- PA release from the stents which contain chitosan microspheres was slower than the only PA incorporated ones. Adding microspheres instead of drug only, was extended the release.

- The stents formulated with PLGA (75:25) polymers were considered to be more promising.

Thank You

This study was supported by
Hacettepe University Scientific Research Unit
(H.U.S.R.U),
Project Number: 0302301007)